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Original Research

Evaluation of the natural history of cancer of the cervix, implications for prevention. The Cancer Risk Management Model (CRMM) – Human papillomavirus and cervical components

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ABSTRACT

The Cancer Risk Management Model (CRMM) initiative of the Canadian Partnership Against Cancer offers policy makers a tool for making decisions regarding prevention and screening for their particular landscape.

The cervical cancer component of CRMM is complex because the development of cervical cancer depends on HPV infection and has to take account of the fact that individuals must come in contact with one another for HPV to spread. Two tightly coupled models were built, one for the infectious spread of HPV (CRMM-HPV), and the other for the pathway from infection to disease onset, progression, screening, treatment, and mortality (CRMM-Cervical). This paper provides an overview of methods and functionality for CRMM components which simulate vaccination, screening, HPV incidence, disease progression, and cancer incidence.

CRMM-HPV is a continuous-time, interacting-agent, Monte-Carlo microsimulation model that simulates sexual networks and HPV transmission. Six HPV groups (6, 11, 16, 18, other non-carcinogenic, other carcinogenic) and two vaccination types (bivalent, quadrivalent) were modeled. Input parameters include demography, sexual debut, partnership formation/separation and virus transmission, clearance, natural immunity. CRMM-HPV provides a 100-year projection of impacts of vaccinations on HPV infections. Results were scaled to reflect the Canadian population aged 10+ in 2011.

Various vaccination scenarios can be compared by altering vaccination program design (target age, sex, program years, participation rate, vaccine type), vaccine efficacy, duration of protection and previous vaccination status. These parameters enable users to explore impacts of various scenarios such as targeting various age groups, adding boys, and booster and catch-up programs.

Introduction

Canada shares with Finland and the United States the distinction of an 80% reduction in mortality from cancer of the cervix as a result of the application of cytology screening [1]. However, in contradistinction to Finland, this has been achieved following a very substantial investment in resources, largely because of the generally accepted view that screening should begin soon after the initiation of sexual activity, and be annual. In contrast, in the organized program in Finland women age 30–59 are screened every five

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years. Detailed analysis of Canadian data has pointed to the rarity of cervix cancer and the lack of effectiveness of cytology screening in young women [2,3]. A working group of the International Agency for Research on Cancer concluded that screening should not begin until age 25 or more [4].

Canada was one of the first countries to initiate screening with cervical cytology. The first program began in British Columbia in 1949 [5] and programs gradually extended across the country. In the mid 1970s, it was shown that the extent of the reduction in cervical cancer mortality was dependent on the intensity of screening [6], and a succession of national Task Forces recommended several measures to increase the effectiveness and efficiency of screening by introducing fully organized programs [7–9]. As the response of the provinces and territories to these recommendations was patchy, a pan-Canadian Cervical Screening Network was initiated in 2004 to foster collaboration and support for the recommendations.

The Canadian Partnership Against Cancer initiated its Cancer Risk Management Model (CRMM) initiative during its first 5-year mandate [10]. The initial priorities were the development of a microsimulation model to evaluate the future burden of cancer in Canada, focusing on areas where it was felt progress could be made. The first two disease-specific models completed were on lung and colorectal cancer [11,12]. In view of the major investment in screening for cancer of the cervix in Canada it was decided that a model for cervical cancer could provide input into the development of policies for organized screening and dovetail into the policy of promoting vaccination of teenage girls against human papillomavirus (HPV) types 16, 18, 6 and 11, initiated in Canada in some provinces in 2007 (Nova Scotia, Ontario and Prince Edward Island), others in 2008 (Alberta, British Columbia, Manitoba, New Brunswick, Quebec, Saskatchewan) and the North West Territories and the Yukon in 2009.

Cancer of the uterine cervix is unique among cancers as it has a single necessary cause, infection with an oncogenic human papillomavirus (HPV) [13]. Such infection is not sufficient for cancer to occur. Other co-factors including parity, smoking, oral contraceptive use, and possibly other infections of the female genital tract, interact in various combinations with the necessary cause to induce the development of cancer. However, the considerable amount of information now available on HPV prevalence, HPV infection by age, and the extent to which such infections become persistent or are cleared by natural immune mechanisms make it possible to model HPV infection and the incidence of cervical cancer, as well as its occurrence via preclinical precursors. It is also possible to estimate the likely cost-effectiveness of different approaches to vaccination against HPV infection, screening and treatment.

The cervical cancer model in CRMM is more complex than the lung and colorectal cancer models [11,12] because the development of cervical cancer depends on HPV infection and individuals must come in contact with one another for the disease to spread. For cervical cancer two coupled models were built, one for the infectious spread of HPV within a population, including the effects of vaccination (CRMM-HPV) and the other for the pathway from infection to disease onset, progression, screening, treatment, and mortality (CRMM-Cervical). This approach allowed the simulation of large interacting populations without sacrificing detail and accuracy in disease progression, screening, treatment, costs, mortality from cervical cancer, and other cause mortality.[1]

CRMM-HPV is an interacting agent model which simulates the process of HPV transmission through sexual interactions in a dynamic network of male–female partnerships, accounting for evolving sex and age-dependent patterns of partnership formation, dissolution, and duration. Detailed HPV infection rates from this simulation are then input into CRMM-Cervical to initiate infections in the isolated simulated individuals in that model. CRMM-Cervical models subsequent cervical precursor lesion incidence and progression in infected individuals. CRMM-Cervical is a non-interacting agent model which simulates treatments, health and economic impacts, and evaluates the impact of different approaches to vaccination, screening, and treatment. Processes which do not involve interaction between individuals are modeled identically in CRMM-HPV and CRMM-Cervical. These include sexual debut, vaccination, HPV clearance, natural immunity, and infection persistence.

The present paper describes the assumptions for CRMM-HPV, their validation and the methodology applied in developing the resultant model; and the results of incorporating this natural history model into CRMM-Cervical to simulate the effects of HPV vaccination.

Materials and methods

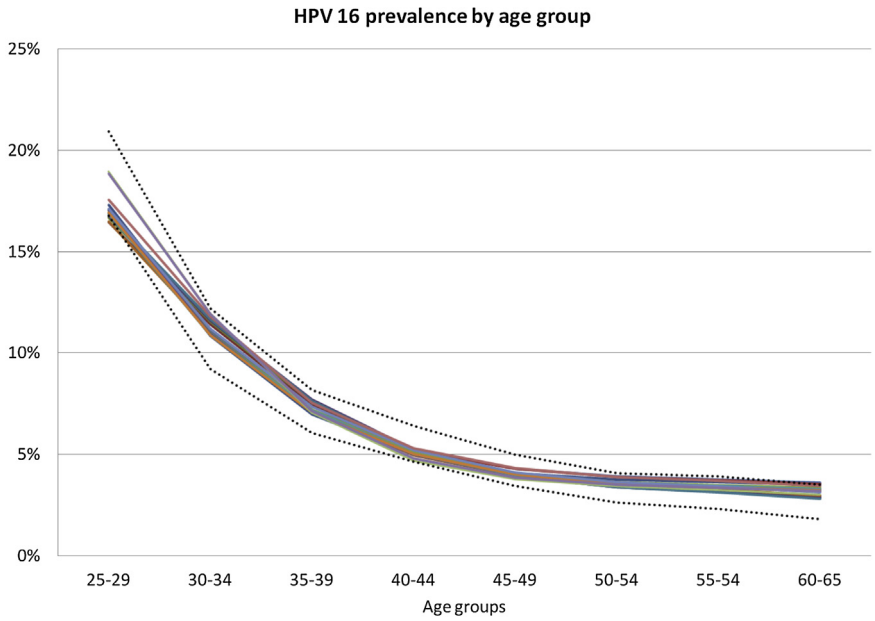
The CRMM, a web-based microsimulation tool, was used to create customized Canadian population-based scenarios that model infection and clearance of HPV and progression/regression through pre-clinical cervix cancer states and ultimately to invasive cervical cancer.

Data to populate the model has been obtained from published and unpublished sources. A working group on cervical cancer (the present authors) was established, and a series of consultations were held with national and international experts. The development work was largely performed by SG and the Statistics Canada team.

CRMM-HPV was developed along similar lines to that of van de Velde et al. [16]. The features of CRMM-HPV include:

- Non-sexually active individuals enter the simulated population at 10 years of age. The model represents an open stable population where the rate of entry into the population balances age and sex-specific Canadian death rates.
- Both stable and casual sequential monogamous partnerships are modeled. Girls and boys are assigned a sexual activity level and become sexually active at a given age by fitting the model to empirical data on sexual debut. Once sexually active, single females form new partnerships at a rate based on age and level of sexual activity. The male partner is chosen from the single male population based on age, activity level, and onset of male sexual debut. Stable partnerships dissolve at rates based on female age and sexual activity level.
- The model represents the transmission and natural history of HPV types 16 and 18 separately, as well as a composite category consisting of all other high-risk HPV types. Low risk HPV types 6, 11, and a composite category of remaining low risk types are also represented.
- The probability of HPV transmission from an infected individual to his/her susceptible partner is modeled per sex act. Consequently, the probability of transmission per partnership is age and level of sexual activity-specific, as it depends on the frequency of sex acts per unit time and the duration of the partnership.
- Virus natural history is modeled to incorporate multiple viral types, per-act transmission and clearance of HPV, natural acquired immunity and persistent infection.
- The duration and the degree of the vaccine effectiveness can be specified by the user, as well as other characteristics of the vaccination program such as targeted ages, sex, and program roll-out.

[1] CRMM-HPV and CRMM-Cervical are freely available. Interested users can access the models through: www.cancerview.ca/cancerriskmanagement after completing a straightforward sign-up process.



Dotted lines indicate upper and lower bounds of fit target. Solid lines refer to model output, each simulated from one of the 16 input parameter vectors estimated using a Bayesian approach discussed in Method section. Note that all solution points fell within the fit target bounds shown above during the parameter estimation process. Some of the simulated solution points in the chart fall outside this target bounds. This is due to Monte Carlo variation between the simulations used to produce the chart and those used during estimation.
Source: CRMM-HPV version 1.7.1.0

Fig. 1. Fit of modeled HPV prevalence. Dotted lines indicate upper and lower bounds of fit target. Solid lines refer to model output, each simulated from one of the 16 input parameter vectors estimated using a Bayesian approach discussed in Method section. Note that all solution points fell within the fit target bounds shown above during the parameter estimation process. Some of the simulated solution points in the chart fall outside this target bounds. This is due to Monte Carlo variation between the simulations used to produce the chart and those used during estimation.
Source: CRMM-HPV version 1.7.1.0.

The model was implemented as follows:

- The event-based microsimulation model was written using the programming language Modgen developed by Statistics Canada.[2]
- A 100-year evolution is included at the start of all simulations to obtain a stable behavioral network and viral transmission patterns.
- This is followed by a 100-year simulation of a vaccination intervention.
- The typical simulation size is 250,000 interacting persons. Sixteen independent simulations, each based on a systematically selected parameter vector from the posterior distribution, are performed to assess the statistical reliability of results. Altogether, approximately 2.1 billion events are simulated in each run.

The behavioral and HPV natural history parameters of CRMM-HPV were estimated using a Bayesian approach with rejection sampling, as described in van de Velde et al. [16], with some modifications. The result is a sample of parameter vectors from the posterior distribution. When the model is run with any member of that sample, outputs satisfy constraints imposed by empirical aggregate data (Fig. 1 shows an example of fit result). These constraining data were obtained from surveys of sexual behavior [17], screening programs [5,6], clinical trials [14], and from additional empirical sources described in [16].

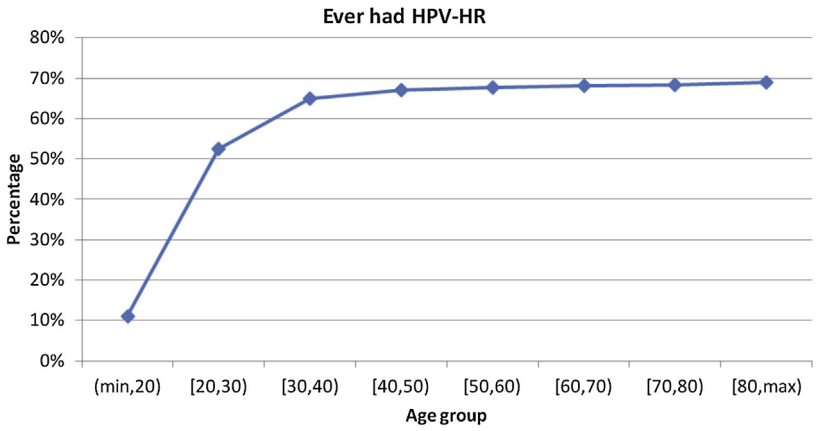
It was initially decided to attempt to fit the model using HPV prevalence rates as documented by Moore et al. [14]. However the estimation procedure for CRMM-HPV was not able to match with data from the Moore study for younger and older age groups. Subsequently, unpublished data were obtained on HPV prevalence from an ongoing Canadian screening trial evaluating HPV DNA tests vs. cervical cytology (the HPV FOCAL trial) [15]. The fitting procedure was able to successfully estimate HPV transmission, clearance and persistence rates consistent with HPV prevalence by age from the Focal trial.

The initial fit of modeled HPV prevalence did not fit well with published data. A number of steps were then taken to modify the modeled prevalence. These steps included:

- Aligning natural immunity with data published by Van de Velde et al. [16] to derive estimated probability of life-long immunity at infection clearance.
- Adding parameters to represent persistent HPV infection resulting in estimated probability that a person will be unable to clear HPV if they are infected.
- Using the HPV-high risk prevalence by age from the Focal trial as a key empirical constraint.
- Using the HPV target prevalence from Moore et al. [14] rather than from Van de Velde et al. [16] to estimate HPV-16 prevalence by age from the HPV Focal trial, and estimate the prevalence of other HPV strains, consistent with the Focal trial. As a result, a much closer fit with published data was achieved (Fig. 1).

CRMM-Cervical simulates disease progression and remission through a sequential series of clinical phases. HPV high-risk infection is required to progress from one phase to the next. Phase-to-phase progression and remission rates were estimated by

[2] http://www.statcan.gc.ca/microsimulation/modgen/modgen-eng.htm.



Simulation of 250,000 interacting agents. HPV-HR indicates HPV infection with any high-risk type.
Source: CRMM-HPV version 1.7.1.0

Fig. 2. Simulated prevalence of those ever infected with an oncogenic HPV type. Simulation of 250,000 interacting agents. HPV-HR indicates HPV infection with any high-risk type.
Source: CRMM-HPV version 1.7.1.0.

calibrating the model using empirical data on prevalence by disease phase, in the context of historical screening and treatment programs. Results after calibration are consistent with observed incidence rates and staging as recorded in the Canadian Cancer Registry.

Vaccination program strategies are specified in detail in CRMM-HPV. The impact of vaccination on HPV incidence is passed from CRMM-HPV to CRMM-Cervical so that full simulations from vaccination to HPV incidence to cervical cancer can be conducted and evaluated. The two-model approach was adopted to maximize available computational power under two different modeling architectures: CRMM-HPV simulates infectious disease where the contact network and transmission of HPV is a central component, which is very computer memory intensive and limits the size of the interacting-agent population; CRMM-Cervical models the cancer where contacts do not play a role, which allows agents to be simulated independently and for very large simulation sizes. Further, the CRMM-Cervical population is representative of the Canadian population, whereas the CRMM-HPV population is a demographically stationary population.

Specific aspects of potential HPV vaccination programs in the model include type of vaccine, e.g. bivalent or quadrivalent, the age to vaccinate, whether the program would be restricted to girls or include boys, whether a catch-up program at later ages would be used, the coverage of the program, its effectiveness, including immunity duration (i.e. lifelong vs. waning) and the effect of revaccination at a later age.

Examples of HPV vaccination strategies simulated here to illustrate functionality include:

- Target 12 year olds starting in 2007 at a coverage rate of 70% each year, the first vaccinated cohort reaches age 25 in the year 2020.
- The effect of adding vaccination of boys of similar ages.
- Increasing the coverage among girls to 90%.

Simulations were performed using CRMM-HPV version 1.7 and CRMM-Cervical version 2.1.

The HPV target prevalence from Moore et al. [14] rather than from Van de Velde et al. [16] was used to estimate HPV-16 prevalence by age from the HPV Focal trial, and the prevalence of other HPV strains, consistent with the Focal trial. As a result, a much closer fit with published data was achieved (Fig. 1).

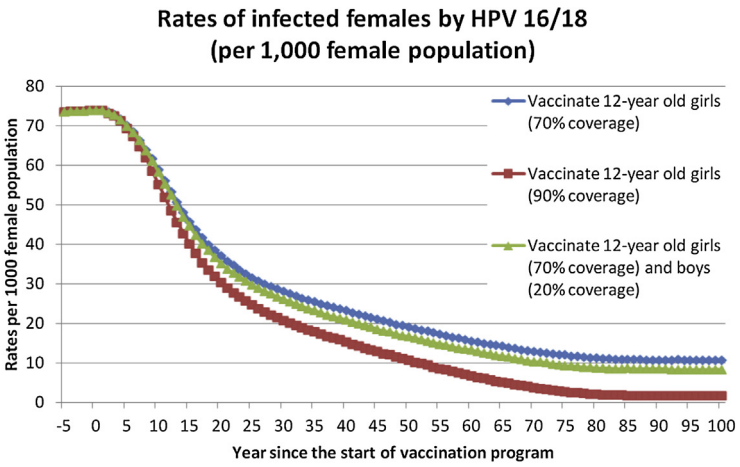
Results

The (simulated) proportion of the female population which has ever had an HPV-HR infection (i.e. any cancer-causing type) so far in their lifetimes is depicted in Fig. 2. In the simulation, HPV infection from high-risk types is highly prevalent in younger women so that by 30 years-old, 65% of females have been previously infected. The proportion plateaus at 70% in the simulation.

An example of the modeled impact of the effect of vaccination of girls at age 12 with 70% coverage and protection continued indefinitely on the number of females infected with HPV 16 and/or 18 is given in the upper curve in Fig. 3. The initial impact is small, and not detectable until about 3 years after vaccination, reaches a maximum at about year 50, and then persists at that level. Similar time relationships are seen for two other vaccination scenarios. However, it is apparent that a greater effect was simulated from vaccinating 90% of the eligible population of girls, than trying to supplement lack of participation of girls by vaccinating a smaller proportion of similar aged boys. The impact on cervical cancer incidence for a range of other scenarios, with variation of participation in vaccination of girls aged 12 are summarized in Table 1. Generally, the simulation shows that the impact of vaccination on cervical cancer incidence is modest over the 40-year period following vaccination.

Discussion

Important health policy decisions can be greatly aided by information on the likely prospective impact of alternative cancer control interventions. The relevant policy scenarios often involve situations where conventional empirical calculations are insufficient. Policy scenarios like various HPV vaccination options are simply too complex, and involve too many different factors. As a result, simulation modeling is becoming the method of choice. Simulation models are able to bring together many diverse strands of empirical evidence in a way that produces relevant outputs, where the assumptions are made explicit, and where parameters for which a strong empirical basis is lacking can be varied in sensitivity analyses. The HPV and cervical components of CRMM have been developed to facilitate decision making in precisely this way. This is important in Canada where the provinces, which have jurisdiction over health care, may have different cervical cancer



Simulation of 250,000 interacting agents; Vaccinating girls (and boys) annually with quadrivalent vaccine; Vaccine efficacy was set to be perfect (100% lifetime protection); Negative vaccination program years indicate pre-vaccination years.
Source: CRMM-HPV version 1.7.1.0

Fig. 3. Influence of vaccination of girls and boys on rates of females infected by HPV 16/18 (per 1000 female population aged 10 years and older). Simulation of 250,000 interacting agents; Vaccinating girls (and boys) annually with quadrivalent vaccine; Vaccine efficacy was set to be perfect (100% lifetime protection); Negative vaccination program years indicate pre-vaccination years.
Source: CRMM-HPV version 1.7.1.0.

Table 1
The effect of varying participation in vaccination and cytology screening on the incidence of cervical cancer.

Vaccination participation[a]	Participation in cytology screening[b]	Cumulative incidence per 100,000 from 2015 to 2050
None	None	15.8
70%	None	13.0
None	80%	7.6
70%	80% in unvaccinated	6.7
50%	80%	6.5
70%	80%	6.2
90%	80%	5.9

Source: CRMM-HPV version 1.7.1.0 and CRMM-Cervical version 2.1.3.0.

[a] Vaccinations were simulated in CRMM-HPV with the simulation of 250,000 interacting agents. The vaccination programs targeted 12-year old girls annually with quadrivalent vaccine of various participation rates. Vaccine efficacy was set to be perfect (100% lifetime protection). The vaccination program assumed to begin in 2008.

[b] Cytology screening and cervical cancer incidence were simulated in CRMM-Cervical with the simulation of 32 million cases and scaled to the size of the Canadian population. Cytology screening in all scenarios is given 3-yearly at ages 21–69 starting from year 2013. Cytology screening prior to 2013 are given every 1–2 years at ages 16–65 at historical levels of participation.

incidence rates and resource capacity. This may require the adoption of different policies for the implementation of vaccination and screening programs.

Vaccination of girls age 10 or more against infection with HPV 16 and 18 has been increasingly accepted across Canada, with varying rates of uptake. Although in the present paper we have modeled various scenarios for Canada as a whole, it is anticipated that the model will eventually be applied on a provincial basis.

The results presented here are preliminary, and will be expanded in a subsequent manuscript using CRMM-Cervical to investigate incidence and mortality endpoints, as well as costs, health benefits and cost-effectiveness of different approaches to screening (Popadiuk et al., in preparation). However, already it is apparent that the major benefit from vaccination on incidence of the disease will not be seen for 40 years.

High compliance with screening is essential to obtain an important impact upon incidence of the disease. In this application of CRMMCervical, we have assumed an 80% participation rate in cervical screening in the last 3 years is achieved, as is the case in Canada currently [18]; such high compliance is sought to ensure that as many as possible of the high-risk group are screened.

One current limitation to the model is that we do not have estimates for health-related quality of life (HRQL) indicators associated with pre-cancerous lesions or any potential impact to HRQL resulting from cervical cancer screening and treatment. Also, to date we have not incorporated the effect of vaccination on other HPV related cancers. But these can be incorporated in future iterations of the model as can the impact of new, e.g. nonavalent vaccines.

In conclusion, CRMM is a powerful, accessible and user-friendly tool. A wide variety of vaccination policy scenario projections can be compared by altering only a few parameters. The platform allows researchers and policy makers to run a complex model in a simple and flexible manner via the internet, to support policy-makers in a readily understandable manner.

Conflicts of interest

None.

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CRMM-HPV was initially developed using information available in the technical appendix of van de Velde et al. [16], aided by input from Marc Brisson.

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